## REMARKS

**Amendments**

Claims 1 and 13-17 are amended to recite bone conditions and disease from claims 5 and 8. As a result, claims 3-4 are cancelled. Claim 5 is amended to depend from claim 2 and is amended to be consistent with the language of claim 1. Claims 6 and 8 are also amended to be dependent on claim 2. Use claims 20, 21, and 25 are cancelled. Claims 23 and 24 are amended to be directed to methods of managing or treating bone disease. New claims 38-40 are directed to further aspects of the invention. See, e.g., page 5, lines 4-12.

**Rejections Under 35 USC §112, second paragraph, and Under 35 USC §101**

Use claims 20, 21, and 25 are cancelled by the above amendments as being redundant with other claims, thereby rendering these rejections moot. Withdrawal of the rejections is respectfully requested.

**Rejection Under 35 USC §102(b) Hutchinson et al.**

Claims 1-5, 9-11, 13-17, 23-24, 26-32, and 34-35 are rejected as being allegedly anticipated in view of the Hutchinson et al. article. This rejection is respectfully traversed.

Hutchinson discloses administering multiple doses up to 4.5 g of "lanthanum" daily to healthy male volunteers. See page S410, left column. Hutchinson disclose that the result was that phosphate excretion decreased. See Figure 1. The form of "lanthanum" administered is not disclosed, but the cited article refers to lanthanum carbonate in its title. See reference no. 22.

Hutchinson further discloses administering lanthanum carbonate to continuous ambulatory peritoneal dialysis (CAPD) patients. This study was said to "confirm the tolerability and efficacy of lanthanum carbonate as a phosphate binder." A sub-group of the study showed a decrease in serum phosphate. See reference no. 23.

In the rejection, it is asserted that the CAPD patients of Hutchinson were "at risk for osteodystrophy and various other bone disorders." However, Hutchinson et al. do not disclose or suggest administering a lanthanum compound to a mammal having a bone fracture, bone trauma, or a bone deficit condition associated with post-traumatic bone surgery, post-prosthetic joint surgery, post-plastic bone surgery, post-dental surgery, bone chemotherapy treatment or bone

radiotherapy treatment, and/or a bone remodeling disorder selected from the group consisting of osteoporosis, Paget's disease, osteoarthritis, rheumatoid arthritis, achondroplasia, osteochodrytis, hyperparathyroidism, osteogenesis imperfecta, congenital hypophosphatasia, fibromatous lesions, fibrous displasia, multiple myeloma, abnormal bone turnover, osteolytic bone disease, osteomalacia and periodontal disease.

Thus, Harris et al. fails to anticipate applicants' claim 15. Withdrawal of the rejection is respectfully requested.

**Rejection Under 35 USC §102(b) in view of Shankar et al.**

Claim 15 is rejected as being allegedly anticipated in view of the Shankar et al. article. This rejection is respectfully traversed.

Shankar et al disclose a study in which the femora and tibiae were removed from newborn Wistar rats. Osteoblasts were mechanically disaggregated by curetting the bones into heat-inactivated foetal calf serum and then agitating the resultant suspension. The osteoclasts were recovered as sediment. The osteoclasts on glass coverslips were exposed to $LaCl_3$. See text bridging pages 907-908. In the Discussion section, Shankar et al. state that "We found that exposure of **isolated** osteoclasts to micromolar [$La^{3+}$] resulted in a concentration-dependent receptor activation leading to an elevation of cystolic [$Ca^{2+}$]." (emphasis added) At page 907, Shankar et al. state that "increased cystolic [$Ca^{2+}$] results in marked inhibition of osteoclastic bone resorption."

It is evident that the study reported by Shankar et al. is an *in vitro* study on osteoclasts removed from the bones of newborn Wistar rats. Shankar et al. provide no disclosure or suggestion of administering $LaCl_3$ to a mammal to contact osteoblasts and inhibit differentiation thereof, particularly in a mammal having a bone diseases or a bone fracture, bone trauma, or a bone deficit condition associated with post-traumatic bone surgery, post-prosthetic joint surgery, post-plastic bone surgery, post-dental surgery, bone chemotherapy treatment or bone radiotherapy treatment, and/or a bone remodeling disorder selected from the group consisting of osteoporosis, Paget's disease, osteoarthritis, rheumatoid arthritis, achondroplasia, osteochodrytis, hyperparathyroidism, osteogenesis imperfecta, congenital hypophosphatasia, fibromatous lesions, fibrous displasia, multiple myeloma, abnormal bone turnover, osteolytic bone disease, osteomalacia and periodontal disease. Shankar et al., thus, fails to describe each element of

applicants' method claim 15.

In view of the above remarks, it is respectfully submitted that Harris et al. fails to anticipate applicants' claims 1-5, 9-11, 13-17, 23-24, 26-32, and 34-35. Withdrawal of the rejection is respectfully requested.

**Rejection Under 35 USC §102(b) in view of Harris et al.**

Claims 1, 13-17, and 23-24 are rejected as being allegedly anticipated in view of the Harris et al. article. This rejection is respectfully traversed.

Harris et al. disclose a study on, among other things, the *in vitro* effect of $LaCl_3$ on calcification. In the *in vitro* portion of the study, tibiae were removed from rachitic rats and placed in a calcifying solution containing sodium chloride, potassium chloride, sodium bicarbonate, calcium chloride, and a combination of $NaH_2PO_4 \cdot H_2O$ and $Na_2HPO_4$. Before being exposed to the calcifying solution, the bones were shaken with $LaCl_3 \cdot 6H_2O$. Calcification was measured by examining the bones for deposits on the epiphyseal plate. Harris et al. state that the results shown in Table 1 show that $LaCl_3$ provided enhancement of calcification *in vitro*.

At page 276, Harris et al. note that $LaCl_3 \cdot 6H_2O$ caused calcified skin wheals in normal rats at the site of injection. When $LaCl_3 \cdot 6H_2O$ was administered to rats on a rachitogenic diet for one day, the occurrence of calcified skin wheals occurred in 50% of the population. When $LaCl_3 \cdot 6H_2O$ was administered to rats on a rachitogenic diet for 24 or 51days, no calcified skin wheals occurred.

Harris et al. provide no disclosure or suggestion of administering $LaCl_3 \cdot 6H_2O$ to a mammal having bone diseases or a bone fracture, bone trauma, or a bone deficit condition associated with post-traumatic bone surgery, post-prosthetic joint surgery, post-plastic bone surgery, post-dental surgery, bone chemotherapy treatment or bone radiotherapy treatment, and/or a bone remodeling disorder selected from the group consisting of osteoporosis, Paget's disease, osteoarthritis, rheumatoid arthritis, achondroplasia, osteochodrytis, hyperparathyroidism, osteogenesis imperfecta, congenital hypophosphatasia, fibromatous lesions, fibrous displasia, multiple myeloma, abnormal bone turnover, osteolytic bone disease, osteomalacia and periodontal disease. Harris et al., thus, fails to describe each element of applicants' method claims 1, 13-17, and 23-24.

In view of the above remarks, it is respectfully submitted that Harris et al. fails to

anticipate applicants' claims1, 13-17, and 23-24. Withdrawal of the rejection is respectfully requested.

**Rejection Under 35 USC §103**

Claims 1-19, 23-24, 26-32, 34-37 are rejected as being allegedly being obvious in view of the combination of the Hutchinson et al. article and the Fernandez-Gavarron et al. article. This rejection is respectfully traversed.

Hutchinson et al. is discussed above. Fernandez-Gavarron et al. disclose an *in vitro* study on the incorporation of lanthanum into teeth, bone and synthetic hydroxyapatite. In its Conclusions at page 290, Fernandez-Gavarron et al. state that during acid-dissolution materials preloaded with lanthanum released less calcium and phosphate in comparison to those that were not treated with lanthanum. In the Summary, Fernandez-Gavarron et al. state that this increased acid resistance may be due to exchange of lanthanum for calcium in the apatite matrix. In the Introduction bridging pages 283-284, Fernandez-Gavarron et al. state that lanthanum ions "could displace some of the divalent calcium ions from the surface of the hydroxyapatite crystal unit cell, yielding structures with new and desirable properties (harder and less acid soluble)." , Fernandez-Gavarron et al. present no results showing increases in strength.

Taking the disclosures together, the *in vitro* results of Fernandez-Gavarron et al. at best merely provide a possible suggestion as to why the subgroup of the 10 CAPD patients discussed by Hutchinson et al. showed a decrease in serum phosphate, i.e., lanthanum was incorporated into bones of the patients resulting in less phosphate being released from those bones. But, this is pure speculation. There is nothing to suggest that lanthanum was actually incorporated into bones of the patients, nor is there anything to suggest that the prior higher serum phosphate concentrations in the patients was in somehow related to acid-dissolution of the bones, i.e., the conditions to which the bones were exposed by Fernandez-Gavarron et al.

Fernandez-Gavarron et al. make mention of exploring clinical usefulness of lanthanum and mentions osteoporosis and aveolar bone resorption (see page 291). However, these *in vitro* at best only suggest further study. Nothing within the disclosure of either Fernandez-Gavarron et al. or Hutchinson et al. would suggest that the results on serum phosphate in a group of 10 CAPD patients would motivate one of ordinary skill in the art to a method of treating a patient in accordance with, for example, applicants claim 1, by administering a lanthanum compound as

recited.

The mere ability to modify a disclosure, in and of itself, to modify the disclosure of a reference does not establish obviousness. See, e.g., *In re Laskowski*, 10 USPQ2d 1397 (Fed. Cir. 1989). Instead, the may must be some motivation that would lead one to modify the disclosure of the reference. No such motivation exists to modify the disclosure of Hutchinson et al. so as to arrive at an embodiment in accordance with applicants' claimed invention. Further, an assertion of "obvious to try" is not a valid basis for obviousness under 35 USC 103. See, e.g, *In re Dow Chemical,* 5 USPQ2d 1529 (Fed. Cir. 1988).

In the rejection, reference is made to an expectation by Fernandez-Gavarron et al. of strengthening bones. As noted above, Fernandez-Gavarron et al. do not presents results showing increased strength, nor is there any indication that the incorporation of La into bones demonstrated by Fernandez-Gavarron et al. would provide *in vivo* treatment of diseases.

Concerning dosages, the disclosure of Hutchinson et al. of up to 2.25 g per day does not suggest the dosage regimes recited in applicants' claims. Nor is there any suggestion that lower dosages would achieve the effect noted by Hutchinson et al. lower serum phosphate.

Finally, the rejection argues that one of ordinary skill in the art would recognize that lanthanum carbonate hydrates are equivalent to lanthanum carbonate. No basis is provided for this assertion. The rejection provides no rationale as to why one upon reading the disclosure of Hutchinson et al. would consider lanthanum carbonate hydrates to be equivalent to lanthanum carbonate in the context of the study discussed by Hutchinson et al.

In view of the above remarks, it is respectfully submitted that Hutchinson et al. and Fernandez-Gavarron et al., taken alone or together, fail to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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